

I. SYNTHESIS OF TETRAHYDROCANNABINOL
II. STUDY OF SOME
POLYHYDROXYNAPHTHALDEHYDES
III. MONOCROTALIC ACID

BY

ZENO WATERBURY WICKS, JR.

A. B., Oberlin College, 1941

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE UNIVERSITY
OF ILLINOIS, 1944

URBANA, ILLINOIS

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I

SYNTHESIS OF TETRAHYDROCANNABINOL

INTRODUCTION

In recent years there have been considerable advances made in the study of the chemistry of the oil derived from *Cannabis sativa*, Adams and co-workers have rigidly proved the structure of cannabinol,¹ isolated cannabidiol,² isomerized it to two isomeric, physiologically-active tetrahydrocannabinols,³ and proved its structure except for the final placement of one double linkage.⁴ Also a large number of synthetic tetrahydrocannabinols and similar substances have been prepared, all of which differ by having a conjugated, rather than a non-conjugated, double bond; these have been shown to have marihuana-like activity but in smaller degree than those prepared from the naturally occurring cannabidiol. The object of this research was to synthesize a tetrahydrocannabinol with a non-conjugated double bond and compare its biological activity and its ultraviolet absorption spectrum with "natural" tetrahydrocannabinol.

DISCUSSION OF RESULTS

The first work undertaken in collaboration with W. D. McPhee and R. B. Carlin was an investigation of the addition of dienes to coumarin and certain substituted cinnamic acids. It was shown that at high temperature, 265°, 2,3-dimethylbutadiene would add to coumarin with the formation of a pyrone, 8-9-dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone. *trans-o*-Hydroxycinnamic acid was shown to be capable of adding 2,3-dimethylbutadiene much more readily, at 185°, to give the same pyrone. The pyrone obtained by the demethylation of the adduct of *trans-o*-methoxycinnamic acid and 2,3-dimethylbutadiene⁵ was shown to be stereoisomeric with the pyrone from coumarin since each was dehydrogenated to give the same dibenzopyrone.

In order to synthesize the tetrahydrocannabinol with a non-conjugated double bond, methyl 1-methyl-5-(2,6-dimethoxy-4-n-amyphenyl)-1-cyclohexene-4-carboxylate, prepared by the meth-

od of Adams and Carlin,⁶ was treated with methylmagnesium iodide and the product dehydrated with potassium acid sulfate. The product from this reaction was shown to be isomeric with cannabidiol dimethyl ether by ozonolysis and estimation of the formaldehyde formed.⁷ This ether was then demethylated with simultaneous ring closure to give a small yield of an isomer of tetrahydrocannabinol as shown by analysis. The low yield of the product was shown to be due to the cleavage of the starting material to *p*-cymene and olivetol. The isomer of tetrahydrocannabinol had a considerably different absorption spectrum than the synthetic "conjugated" tetrahydrocannabinol, although somewhat different the spectra was quite similar to that of the "natural" tetrahydrocannabinol. The material was shown by bio-assay to have a marihuana potency of 0.5 ± 20 per cent, that is about one half that of the synthetic "conjugated" material and considerably less than that of the "natural" tetrahydrocannabinol.

II

STUDY OF SOME

POLYHYDROXYNAPHTHALDEHYDES

The structure of gossypol, the yellow pigment in cottonseed, has been postulated as 2,2'-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl. The reactions of gossypol are in agreement with this structure, but it is necessary to assume that gossypol has two tautomeric forms. The molecule is very reactive and readily oxidized; for this reason, and because of the many substituents, the synthesis of gossypol for the final proof of structure is impractical. A valuable addition to the proof of the structure would, however, be obtained if a tautomerism similar to that postulated in the case of gossypol could be shown in a simple naphthalene compound. The only groups directly involved in these tautomerisms are the 1- and 7-hydroxyl groups and the 8-aldehydo group, therefore, 2,8-dihydroxy-1-naphthaldehyde would be expected to show tautomerism. However, Adams and Burney⁸ after investigation of the properties of this compound concluded that it did not undergo tautomerism. It was therefore assumed that another group present in the gossypol molecule, probably the hydroxyl group in the 3-position, was

necessary for the tautomerism. The object of this research was to attempt to prepare 2,3,8-trihydroxy-1-naphthaldehyde, or a substituted compound containing these groups, and investigate its tautomerism.

DISCUSSION OF RESULTS

Eight possible methods of synthesis of a molecule containing the grouping present in 2,3,8-trihydroxy-1-naphthaldehyde were attempted and found unsatisfactory. The closest approach to the desired molecule was the preparation of 2,3,5,8-tetramethoxy-6,7-dimethyl-1-naphthaldehyde but it was not possible to demethylate this compound to the corresponding tetrahydroxy-naphthaldehyde. The synthesis was carried out by a Diels-Alder condensation of *o*-xyloquinone with 2,3-dimethylbutadiene. The naphthoquinone thus obtained was reduced to the hydroquinone and the hydroquinone was methylated to give 1,4,6,7-tetramethoxy-2,3-dimethylnaphthalene. The aldehyde was prepared from this compound by treatment with *N*-methylformanilide and phosphorous oxychloride. Demethylation of the intermediate compounds such as 2,3-dimethyl-6,7-dimethoxy-1,4-naphthoquinone was also unsuccessful.

III

MONOCROTALIC ACID

INTRODUCTION

The alkaloid monocrotaline occurs in the seed of the *Crotalaria spectabilis*, the most important of a genus of leguminous plants which are widely used in the southern part of the United States as soil-enriching legumes. Alkaline hydrolysis of monocrotaline yields the base, retronecine, carbon dioxide, and an acid, monocrotic acid, which has been shown to be α,β -dimethyllevulinic acid.⁹ On the other hand, hydrogenolysis of monocrotaline gives the base, retronecanol, and an acid, monocrotalic acid. Since monocrotalic acid apparently occurs in the alkaloid esterified with retronecine, a knowledge of the structure of the acid is essential to a complete knowledge of the structure of the alkaloid. The most recent work of Adams and co-workers¹⁰ has indicated that monocrotalic acid is most probably an optical

isomer of the lactol of γ -keto- α,β -dimethyladipic acid. In the present investigation an attempt has been made to obtain further evidence for this structure.

DISCUSSION OF RESULTS

Since the lactol of γ -keto- α,β -dimethyladipic acid contains a methylene grouping, attempts were made to prove the presence of this grouping in monocrotalic acid and its derivatives; they were, however, unsuccessful.

α,β -Dimethyladipic acid and α,β -dimethylhomolevulinic acid were synthesized and characterized with the hope of comparing them with compounds obtained by the degradation of monocrotalic acid. The degradation of monocrotalic acid to these compounds, however, has not been successfully accomplished.

The synthesis of a derivative of monocrotalic acid was then undertaken. The proposed synthesis involves the cleavage of 2-nitro-3,4-xilenol with hot sulfuric acid to α,β -dimethyl- $\Delta(\alpha,\beta)$ -crotonolactone- γ -acetic acid by the method of Pauly, Gilmour, and Will¹¹ for the conversion of *o*-nitro-*p*-cresol to β -methyl- $\Delta(\alpha,\beta)$ -crotonolactone- γ -acetic acid. This compound then would be an isomer of the proposed structure of anhydromonocrotalic acid and could be converted by hydrogenation to a mixture of stereoisomers of dihydroanhydromonocrotalic acid. After several attempts, the synthesis of 2-nitro-3,4-xilenol was accomplished through the following intermediates: 3,4-xilenol, 4,5-dimethylsalicylic acid, methyl 4,5-dimethylsalicylate, methyl 3-nitro-4,5-methylsalicylate, 3-nitro-4,5-dimethylsalicylic acid. The ring cleavage of the nitrophenol resulted by heating with Grasselli concentrated sulfuric acid to give the desired α,β -dimethyl- $\Delta(\alpha,\beta)$ -crotonolactone- γ -acetic acid.

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VITA

The author was born in Port Jervis, New York, on July 24, 1920. He attended the elementary schools of Toms River, New Jersey, and Akron, Ohio, and was graduated from West High School, Akron, Ohio, in June of 1936. He received the degree of Bachelor of Arts, *summa cum laude*, from Oberlin College in 1941. In the fall of the same year, he entered the Graduate School of the University of Illinois as a teaching assistant in organic chemistry. In the year 1942-1943, he held a University of Illinois fellowship in chemistry, and in the year 1943-1944, the Eastman Kodak fellowship in chemistry.

